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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/500,561 | 03/21/2005 | Yoshiharu Minamitake | 58778.000003 | 7719 |

21967 7590 09/22/2006

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| EXAMINER | |
|---|---|
| GUDIBANDE, SATYANARAYAN R | |
| **ART UNIT** | **PAPER NUMBER** |
| 1654 | |

DATE MAILED: 09/22/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/500,561 | MINAMITAKE ET AL. | |
| | Examiner | Art Unit | |
| | Satyanarayana R. Gudibande | 1654 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/30/04, 1/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Applicant's election with traverse of group II invention and election of acetic acid as a buffer agent and acetate buffer as a buffer solution in the reply filed on 9/7/06 is acknowledged. The traversal is on the ground(s) that there is unity of invention exists between the two inventions and the reference WO 01/92292 does not teach the technical feature of claim 1 because, it only discloses a pharmaceutically acceptable salts of truncated ghrelin. This is not found persuasive because the derivative of ghrelin as recited in claim 1 includes truncated ghrelin molecules, because the truncated version of the molecule is derived from ghrelin itself. Therefore the special technical feature of the group I is not a composition over prior art. Additionally, species requirement was necessary between the ghrelin and its derivatives, buffer agents and solutions because it would be burdensome search to look for different derivatives and different salts of derivatives that are chemically distinct from each other. Search for one species would not lead us to discovery of others while searching non-patent literature.

Therefore, the restriction requirement is still deemed proper and is therefore made FINAL.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsumoto, et al., Biochemical and biophysical Research communications, 2001, 287, 142-146 in view of US 6,967,237 B2 issued to Bednarek, and further in view of Voet, et al., Biochemistry, 1995, II Edition, John Wiley & Sons, Inc., pages 60-62 and 77.

In the instant application, applicants claim a method of preventing degradation of a hydrophobic group of ghrelin or its derivative in a solution with a pH in the range 2 to 7. Applicants also claim acetic acid as pH adjuster and acetate buffer as buffer solution.

Matsumoto, et al., teaches the ghrelin molecule and several other analogs of ghrelin (tables 1-4 in the reference). The reference teaches that altering the charge of the N-terminal and C-terminal residues exhibited altered the activity of the ghrelin molecules. Amidation of the C-terminal carboxylic acid enhanced the activity approximately 8-fold compared to the native ghrelin. Elimination of the positive charges at the N-terminus resulted in lowered ghrelin activity as observed for [$N^{\alpha}$-acetyl]-ghrelin. Hence, the results seen here indicated a role of charge in ghrelin activity and that positive charges are essential in maintaining a high level of activity and negative charges inhibit activity (page 145, column 2, paragraph 1 under the subtitle 'charges of

ghrelin and activity'). The reference also teaches that replacement of an octanoyl ester bond by a more table ether or thioether bond enhances the long-term stability of the ghrelin molecules for pharmaceutical applications and hydrophobicity surrounding the third amino acid residue regardless of the type of hydrophobic moiety is essential for growth hormone secretogogue (GHS) activity (bridging paragraph 2 in column 2, page 145-146). The reference does not teach the use of acetic acid or acetate buffer for maintaining the positive charge on the molecule in solution. Nor does it explicitly mention the pH of the solution.

Bednarek discloses that the truncated ghrelin analogs can be formulated of administering to subjects and ghrelin analogs can be prepared as acidic or basic salts. The pharmaceutically acceptable salts using organic or inorganic acids or bases including the acetate, citrate, succinate, fumarate, lactate, etc., (column 10, lines 20-52). The reference teaches the formation of acid salts of ghrelin derivatives.

Voet, et al., Biochemistry, 1995, II Edition, John Wiley & Sons, Inc., pages 60-62 and 77, discloses that at low pH the acidic and basic functional groups of amino acids such as Glycine are protonated (page 61, column 1, paragraph 1). Proteins being polymers of different amino acids they carry many ionizable groups. At the isoelectric pH of a protein, the net charge on the protein is neutral and at acidic pH the proteins are protonated.

It would have been obvious to one of ordinary skill in the art to modify the teachings of Matsumoto and Bednarek to develop a method for preventing degradation of a hydrophobic group of ghrelin or its derivative by adjusting the pH of solution in the range of 2-7. Because, Matsumoto teaches that role of maintaining positive charge in the ghrelin molecule is essential for high-level activity of the molecules and such positive charge is maintained by converting the

ghrelin molecule to an acid salt as taught by Bednarek and Voet. The motivation for maintaining the pH in the range 2-7 stems from the fact that the ghrelin, and ghrelin derivatives shows higher activity when it is positively charged as taught by Matsumoto. It is shown by Voet that zwitterionic molecules such as amino acids and proteins with many ionizable groups can be protonated by lowering the pH of the solution for which acetate buffer in the pH range 2-7 is necessary. There would have been reasonable expectation of success given the knowledge that protonated ghrelin molecules would have higher activity combined with the hydrophobicity at the 3$^{rd}$ residue at the N-terminal end. The reasonable expectation of success would have to lead modification of the teachings of Matsumoto, Bednarek and Voet to incorporate the ghrelin molecule in a buffer with pH in the range 2-7. Thus the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time invention was made.

## *Conclusion*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Satyanarayana R. Gudibande, Ph.D.
Art Unit 1654

ANISH GUPTA
PRIMARY EXAMINER